

Short-Course (3-Month) Therapy with Weekly Isoniazid-Rifapentine Is NOT RECOMMENDED for HIV-Infected Patients Receiving Antiretroviral Therapy (December 20, 2011)

The purpose of this supplemental information is to alert clinicians about the use of short-course therapy with weekly isoniazid plus rifapentine (INH-RPT) for the treatment of latent tuberculosis infection (LTBI) in HIV-infected patients. Pharmacokinetic data are lacking on the interactions between RPT and antiretroviral (ARV) drugs; therefore, until such data are available, the Panel recommends the following:

- **HIV-infected patients receiving antiretroviral therapy (ART) SHOULD NOT receive the 3-month weekly INH-RPT regimen for treatment of LTBI, unless given in the context of a clinical trial (AIII).**
- **Patients receiving ART should receive LTBI treatment according to current recommendations in the guidelines for treatment and prevention of opportunistic infections^{1,2} (AI).**
- **HIV-infected patients 12 years of age or older who are not receiving ART can be prescribed either a 9-month INH regimen or the 3-month once-weekly INH-RPT regimen by directly observed therapy (DOT), as recommended in the new Centers for Disease Control and Prevention (CDC) guidelines³. Clinicians should note that data are limited on efficacy and safety of the 3-month regimen in HIV-infected patients (not on ART).**
- **For HIV-infected children 2 to 11 years of age who are not receiving ART, the standard 9-month regimen of daily INH monotherapy is preferable, but the 3-month INH-RPT regimen can be considered on a case-by-case basis. The 3-month INH-RPT regimen is not recommended for children younger than 2 years of age.**

Background

Treatment of LTBI can prevent progression to active TB. INH given once daily for 9 months is the standard treatment regimen for LTBI. In an open-label, randomized non-inferiority trial, a 3-month combination regimen of INH-RPT, given by DOT once weekly, was compared with the standard 9-month self-administered once daily INH regimen for LTBI treatment⁴. The study results included more than 7,000 enrolled subjects. After 33 months of follow-up, in a modified intention-to-treat analysis, 15 cases of TB were diagnosed in the INH recipients and 7 cases in the INH-RPT recipients (hazard ratio: 0.38 for INH-RPT, confidence interval [CI] 0.15–0.99, $P = 0.05$). The permanent discontinuation rate before treatment completion was higher in the INH alone arm. In this study, only 105 HIV-infected patients who were not receiving ART received the 3-month INH-RPT.

The 3-month regimen of INH-RPT has the advantages of shorter treatment duration, higher completion rate, and efficacy non-inferior to INH alone for 9 months. The results of this study have led to a new CDC recommendation¹ in which 3-month once-weekly INH-RPT given by DOT is considered an equal alternative to the standard 9-month regimen for adults and adolescents (≥ 12 years old). This regimen, however, is NOT recommended for HIV-infected patients receiving ART (AIII).

Rationale for NOT Recommending Short Course INH-RPT for Treatment of LTBI in HIV-Infected Patients Receiving ART

RPT is a rifamycin-antibiotic with a long plasma half-life, allowing it to be dosed less frequently than other commonly used rifamycins, such as rifampin and rifabutin. Like other rifamycins, RPT induces the cytochrome P450 enzyme system, which is responsible for the metabolism of many drugs including HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and maraviroc. Rifampin also induces the enzyme UGT-1A1, leading to interaction with raltegravir. No systematic study has been performed to assess the magnitude of the enzyme induction effect of RPT on the metabolism of ARV drugs and other concomitant drugs. Significant enzyme induction can result in reduced ARV drug exposure, which may compromise virologic efficacy.

Pharmacokinetic studies and clinical trials to evaluate the impact of RPT on ART are under way or in the planning stages.

References:

1. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009; 58(RR-4): 1-207.
2. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep.* 2009; 58(RR-11): 1-166.
3. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR* 2011; 60(48): 1650-3.
4. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *New Engl J Med.* 2011; 365: 2155-66.

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The HHS Panel on Antiretroviral Guidelines for Adults and Adolescents and the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, in consultation with:

- The HHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents; and
- The HHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Children

For more detailed information regarding treatment and care for the HIV-infected patient, consult the *AIDSinfo* Web site: <http://aidsinfo.nih.gov/Guidelines/Default.aspx>